

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 11 APR 2006

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Applicant's or agent's file reference S 10019 PCT		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2005/002328		International filing date (day/month/year) 04.03.2005		Priority date (day/month/year) 04.03.2004
International Patent Classification (IPC) or national classification and IPC INV. C07K14/51 C07K14/47 C12N15/12 C12N15/63 C12N5/10 C12P21/00 C07K16/22 A61K38/18				
Applicant JULIUS-MAXIMILIANS-UNIVERSITÄT WÜRZBURG et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 04.10.2005		Date of completion of this report 10.04.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Mabit, H Telephone No. +49 89 2399-7270		



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-37 as originally filed

Sequence listings part of the description, Pages

1-21 as originally filed

Claims, Numbers

1-38 as originally filed

Claims, Pages

1-7 as originally filed

Drawings, Sheets

1-8 as originally filed

Drawings, Figures

1-8 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

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4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

** If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 7, 9-13, 16-17, 20, 22-38 partially
because:
 - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☒ the claims, or said claims Nos. 7, 9-13, 16-17, 20, 22-38 partially are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
 - ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-6, 8, 14-15, 18-19, 21 and claims 7, 9-13, 16-17, 20, 22-38 partially
	No: Claims	
Inventive step (IS)	Yes: Claims	1-6, 8, 14-15, 18-19, 21, and claims 7, 9-13, 16-17, 20, 22-38 partially
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-6, 8, 14-15, 18-19, 21, and claims 7, 9-13, 16-17, 20, 22-38 partially
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☐ received by this Authority as an amendment on
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

Re Item II

Priority

The current assessment is based on the assumption that all claims enjoy the priority rights from the filling date of the priority document (04.03.2004).

The document D1 has been cited as an X document in the International Search Report for claims 1-4 and 14-17.

However, it appears that the date of release of the content of this document was 04.05.2004. Therefore, this document will be considered as a P document and not as an X document.

Should the priority of the application not be valid, D1 and the document Keller et al., cited in the International Search report would be relevant with respect to novelty and inventive step (Article 33(2) and 33(3) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claim 7 relates to products defined by reference to a desirable characteristic or property, i.e. binding properties of the bone morphogenetic mutein.

This claim and the claims related/dependent thereon, i.e. claims 9-13, 16-17, 20, 22-38 partially cover all muteins having this characteristic or property, whereas the application provides support within Art 6 PCT and disclosure within the meaning of Art 5 PCT for only a very limited number of such muteins. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lacks clarity (Art 6 PCT). An attempt is made to define the mutein by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely the parts of claims 7, 9-13, 16-17, 20, 22-38 related to the muteins mentioned in the dependent claim 14.

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Since the search was limited to these compounds, the opinion with respect to novelty, inventive step and industrial applicability will only be established for the subject-matter of the searched claims.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: DATABASE NCBI from human 7 November 2003 (2003-11-07), "Chain A, structure of the Bone Morphogenetic Protein 2 Mutant L51P" XP002297411 Database accession no. 1REUA
- D2: NICKEL J ET AL: "THE CRYSTAL STRUCTURE OF THE BMP-2: BMPR-IA COMPLEX AND THE GENERATION OF BMP-2 ANTAGONISTS" JOURNAL OF BONE AND JOINT SURGERY, JOURNAL OF BONE AND JOINT SURGERY. BOSTON, US, vol. 83-A, no. SUPPL PART 1, 2001, pages S1-7, XP009005357 ISSN: 0021-9355
- D3: KIRSCH THOMAS ET AL: "Crystal structure of the BMP-2-BRIA ectodomain complex" NATURE STRUCTURAL BIOLOGY, vol. 7, no. 6, June 2000 (2000-06), pages 492-496, XP002297408 ISSN: 1072-8368
- D4: GROPE JAY ET AL: "Structural basis of BMP signaling inhibition by Noggin, a novel twelve-membered cystine knot protein." THE JOURNAL OF BONE AND JOINT SURGERY. AMERICAN VOLUME. 2003, vol. 85-A Suppl 3, 2003, pages 52-58, XP009036882 ISSN: 0021-9355

The subject-matter of claims 1-38 appears to be novel (Art 33(2) PCT).

The problem underlying the present application is to provide a mutein of a bone morphogenetic protein which does not bind to a first bone morphogenetic protein receptor but still binds to modulator proteins such as the proteins from the noggin, DAN, and chordin families.

The Document D2 shows that Leucine 51 is situated in the middle of a 6 amino acids sequence involved in the interaction with BMPR-1. Even if the particular amino acid position 51 has not been identified as a critical one, a skilled person would easily suppose that a substitution in the proline residue at position 51 would change the structural positions of the amino acid residues at proximity and therefore would decrease the binding with BMPR-1.

A sentence in D3 points also to the role of the leucine 51 in the binding to the receptor: "While the side chain of leu 51 points into the interior of BMP-2A, both main chain atoms of this residue engage in completely buried hydrogen bonds to the side chain of Gln 86 of BRIA" (page 494, 2nd paragraph).

However, the L51P mutant of the present application surprisingly still binds to modulators. It is mentioned in D4 that Noggin inhibits BMP signaling by blocking the binding sites of both types of receptors, mimicking their modes of binding. Since the L51P mutation destroys the binding site to the receptor, it was not obvious that this mutation will not destroy the binding to noggin.

Therefore, an inventive step can be recognized for the subject-matter of claims 1-38.